Lack of Association Between Acellular Pertussis Vaccine and Seizures in Early Childhood

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KEY WORDS
vaccines, adverse reactions, pertussis, infant

ABBREVIATIONS
DTP— diphtheria-tetanus-whole-cell-pertussis vaccine
DTaP— diphtheria-tetanus-acellular pertussis vaccine
VSD—Vaccine Safety Datalink
MCO—managed care organization
CDC—Centers for Disease Control and Prevention
ICD-9-CM—*International Classification of Diseases, Ninth Revision, Clinical Modification*
ED— emergency department
MMR—measles-mumps-rubella vaccine
MMRV—measles-mumps-rubella-varicella vaccine
SCCS—self-controlled case series
IRR—incidence rate ratio
CI— confidence interval
RR—relative risk

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WHAT'S KNOWN ON THIS SUBJECT: Receipt of DTP is associated with febrile seizures in the immediate postvaccination period. Although the risk for seizures was lower with DTaP than DTP, limited population-based studies have been conducted on the risk for seizures after DTaP vaccination.

WHAT THIS STUDY ADDS: This study used the risk-interval cohort and self-controlled case series analyses to compare the incidence of seizures in the risk and control periods. There was no increased risk for seizures within 3 days after receipt of DTaP in early childhood.

abstract

OBJECTIVES: Receipt of diphtheria-tetanus-whole-cell pertussis vaccine (diphtheria-tetanus toxoids-pertussis [DTP]) is associated with seizures. Limited population-based studies have been conducted on the risk for seizures after receipt of diphtheria-tetanus-acellular pertussis vaccine (diphtheria-tetanus-acellular pertussis [DTaP]).

METHODS: We conducted a retrospective study from 1997 through 2006 by using risk-interval cohort and self-controlled case series (SCCS) analyses on automated data at 7 managed care organizations that participate in the Vaccine Safety Datalink (VSD). Eligible children included the 1997–2006 VSD cohort of patients who were aged 6 weeks to 23 months and had not received DTP during the study period. A seizure event (febrile or afebrile) was defined by *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnoses assigned to an inpatient or emergency department setting. The exposed period was composed of a predefined 4 person-days after each DTaP dose. All of the remaining observation periods outside the exposed periods were categorized as unexposed. The risk-interval cohort method compared the incidence of seizures between the exposed and unexposed cohorts. In the SCCS method, the comparison was performed between the same patient's exposed and unexposed period.

RESULTS: We identified 7191 seizure events among 433 654 children. The adjusted incidence rate ratio of seizures across all doses was 0.87 in cohort analysis and 0.91 in SCCS analysis.

CONCLUSIONS: We did not observe an increased risk for seizures after DTaP vaccination among children who were aged 6 weeks to 23 months. These findings provide reassuring evidence on the safety of DTaP with respect to seizures. *Pediatrics* 2010;126:e263–e269

Receipt of whole-cell pertussis vaccine combined with diphtheria and tetanus toxoids (DTP) has been associated with rare neurologic adverse events, including seizures, in the immediate postvaccination period.[1–4] In the 1970s, concerns among the public and vaccine providers about the safety of DTP led to a decline in immunization coverage and, subsequently, an increase in pertussis disease and deaths in several countries, including the United Kingdom and Japan.[5,6]

In 1997, the Advisory Committee on Immunization Practices recommended the acellular pertussis vaccine combined with diphtheria and tetanus toxoids (DTaP) for routine immunization of infants and young children as a 5-dose schedule at ages 2, 4, 6, and 15 to 18 months and 4 to 6 years.[7] Analyses of the Vaccine Adverse Event Reporting System[8] postlicensure passive surveillance data from 1991 to 1993 and 1995 to 1998 suggested that reports of seizures were less frequent after administration of DTaP compared with DTP or DTP-*Haemophilus influenzae* type b vaccines.[9,10] Using data from the Vaccine Safety Datalink (VSD) Project,[11] Davis et al[12] also retrospectively detected a decrease in the risk for seizures in the 0 to 3 days after vaccination within 42 weeks after the changeover from DTP to routine use of DTaP.

DTaP vaccines (including DTaP component vaccine or combination vaccine [DTaP-*Haemophilus influenzae* type b and DTaP-hepatitis B-inactivated poliovirus vaccines]) are now the only pertussis vaccines licensed in the United States for children.[13] Although the risk for seizures was found to be lower with DTaP than DTP,[9,10,12] limited population-based studies have been conducted to compare the incidence of seizures after DTaP vaccination with the incidence in referent periods unrelated to vaccination. We used the VSD postlicensure cohort to assess the association between DTaP and seizures in early childhood.

METHODS

Study Design and Participants

We used a retrospective cohort to examine the risk for seizures after DTaP vaccination in children who were aged 6 weeks to 23 months. The study cohort included members from 7 of the 8 managed care organizations (MCOs) that collaborate with the Centers for Disease Control and Prevention (CDC) in the VSD Project.[11] The VSD Project uses linked administrative data collected on demographics, enrollment, immunizations, and *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes assigned to inpatient, emergency department (ED), and outpatient medical encounters, for >2.2 million children <18 years of age.[11]

To be eligible for the study, a child had to be enrolled in the MCO within 6 weeks of birth between January 1, 1997, and December 31, 2006, and had to be continuously enrolled for at least 14 days after each dose of DTaP. Follow-up for each study patient began at the time of age 6 weeks and ended at the earliest of the following dates: 23 months old, disenrollment from the MCO, death, or December 31, 2006. Children who during the observation period had been immunized with DTP or had 2 consecutive DTaP doses administered at an interval less than the recommended minimal interval in the catch-up immunization schedule[14] were excluded from the study population.

The institutional review boards at CDC and each of the 7 MCOs approved this study.

Ascertainment of Vaccination Status

Information on administration of DTP and DTaP to eligible children during the observation period was obtained from automated immunization tracking systems that collect data on all routinely administered immunizations. Receipt of measles-mumps-rubella vaccine (MMR) has been associated with an increased risk for febrile seizures in the 8 to 14 days after vaccination.[3,4] A newly licensed combined measles-mumps-rubella-varicella vaccine (MMRV) is also associated with an increased risk for febrile seizures in the 5 to 12 days,[15] in particular 7 to 10 days, after vaccination.[16] Either MMR or MMRV can be used for routine immunization against measles, mumps, and rubella at ages 12 to 15 months.[14] To evaluate for potential confounders, we also collected information on administration of MMR and MMRV to eligible children during the observation period from the immunization tracking system. The data in the tracking system undergo extensive quality review and show high rates of agreement with data obtained from chart reviews.[17]

Ascertainment of Outcomes

Seizure events that occurred in eligible children during the observation period were identified by using ICD-9-CM diagnosis code 333.2 (myoclonus), code 345* (any code with prefix "345"; epilepsy), code 779.0 (convulsions in newborn), code 780.3 (convulsions), code 780.31 (simple febrile convulsions), code 780.32 (complex febrile convulsions), or code 780.39 (other convulsions).[4] For children who were aged 6 weeks to 23 months, the predictive positive value of these seizure codes for true acute seizure events was high in the ED (97%) and inpatient settings (64%) but low in the outpatient clinic setting (16% on days 1–30 after vaccination, 2% for visits on the same day of vaccination)[18]; therefore, we restricted seizure diagnoses to those in association with a hospital discharge or ED visit. Readmissions or revisits within 3 days with any seizure diagnosis were counted as 1 episode.

Statistical Analyses

For testing of the null hypothesis that the incidence of seizures is not different in the 4 person-days after each DTaP dose compared with a control period temporarily unrelated to vaccination, the cohort data set was analyzed by using 2 methods: the risk-interval cohort method and the self-controlled case series (SCCS)[19] method. We categorized each study patient's observation period into exposed and unexposed person-time. Each of the exposed person-time periods, based on the results of studies that assessed the risk for febrile seizures after DTP vaccination,[3,4] was composed of a predefined postvaccination 4 person-days (day 0 to day 3) for each DTaP dose, which, at maximum, would be 4 exposed periods. All of the remaining observation periods outside these exposed periods were categorized as unexposed (referent) person-time. For children who never received DTaP, the whole observation period was considered unexposed.

Risk-Interval Cohort Analyses

In the risk-interval cohort analyses, all study patients' exposed person-time was summarized into the exposed cohort, and their unexposed person-time was summarized into the unexposed cohort. The incidence of seizures in the exposed cohort was calculated by dividing the number of events by the corresponding person-time denominator and compared with the baseline incidence of seizures calculated from the unexposed cohort. Unconditional Poisson regression was used to estimate the incidence rate ratios (IRRs) for seizures during the 0 to 3 days after vaccination and stratified by subintervals (day 0 vs days 1–3) as well as by vaccine dose number (first, second, third, and fourth doses). Gender, MCO, calendar year (1997–1999, 2000–2002, and 2003–2006), season of the year (January to March, April to June, July to September, and October to December), age (≤3, 4–6, 7–9, 10–12, 13–15, 16–18, and 19–23 months), and receipt of MMR or MMRV within 8 to 14 days were adjusted for in the multivariate model.

Self-controlled Case Series Analyses

The SCCS analyses included only children who ever received a diagnosis of seizures during the observation period. In the SCCS method, each patient's exposed person-time was matched to all of the unexposed person-time from the same individual as a separate stratum; therefore, patients with seizures functioned as their own controls, with implicit adjustment for measured and unmeasured confounders that did not vary over time.[19] Analyses were conducted using conditional Poisson regression to estimate the IRRs within the predefined risk intervals (0–3 days, day 0, and 1–3 days after vaccination) by vaccine dose number, with adjustments for calendar year, season, age, and receipt of MMR or MMRV within 8 to 14 days as described in risk-interval cohort analyses. For children who did not receive DTaP but had received a diagnosis of seizures during the observation period, the incidences of seizures in these unexposed person-times were included in the multivariate model to adjust for changes in the baseline incidence of seizures according to age.

All analyses were performed by using SAS 9.1.3 (SAS Institute Inc, Cary, NC).

RESULTS

From 1997 through 2006, a total of 493 489 children who were aged 6 weeks to 23 months met the eligibility criteria. We excluded 33 397 (7%) children who had received DTP and 26 438 (5%) children who had a subsequent dose of DTaP administered at an interval less than the recommended minimal interval. The final study cohort was composed of 433 654 children; 222 470 (51%) were male.

The study cohort received 1 343 067 doses of DTaP during the observation period. Of these, 388 335 (29%), 374 106 (28%), 345 302 (26%), and 235 324 (17%) were administered as the first, second, third, and fourth vaccine doses, respectively. The number of DTaP doses administered and baseline incidence of seizures by months of age are illustrated in Fig 1. At times of DTaP vaccination, the median age was 2 months (range: 1–23) for the first, 4 months (range: 2–23) for the second, 6 months (range: 3–23) for the third, and 15 months (range: 11–23) for the fourth vaccine dose. The baseline incidence of seizures varied by age (Fig 1); the incidence was the lowest at 3 months (582 seizures per 100 000 person-years) and the highest at 16 months (2004 seizures per 100 000 person-years). For children who had received DTaP, the incidence of seizures outside the predefined exposed periods (1208 seizures per 100 000 person-years [95% confidence interval [CI]: 1180–1237]) was not significantly different compared with the incidence of seizures for children who never received DTaP (1083 seizures per 100 000 person-years [95% CI 960–1223]).

We identified 7191 seizures events involving 5205 patients; 112 seizures occurred within 0 to 3 days of receiving DTaP. Of the 7191 events, 4557 (63%) were ED and 2634 (37%) were hospital diagnoses (Table 1). Simple (code 780.31) or complex (code 780.32) febrile convulsions were the most frequent seizure diagnoses coded in the ED (67%) and ED and hospital combined (49%), whereas "other convulsions" (codes 780.39) was the most frequent diagnosis in the hospital (52%).

The unadjusted incidence of seizures in the postvaccination 0 to 3 days was higher after the fourth dose of DTaP

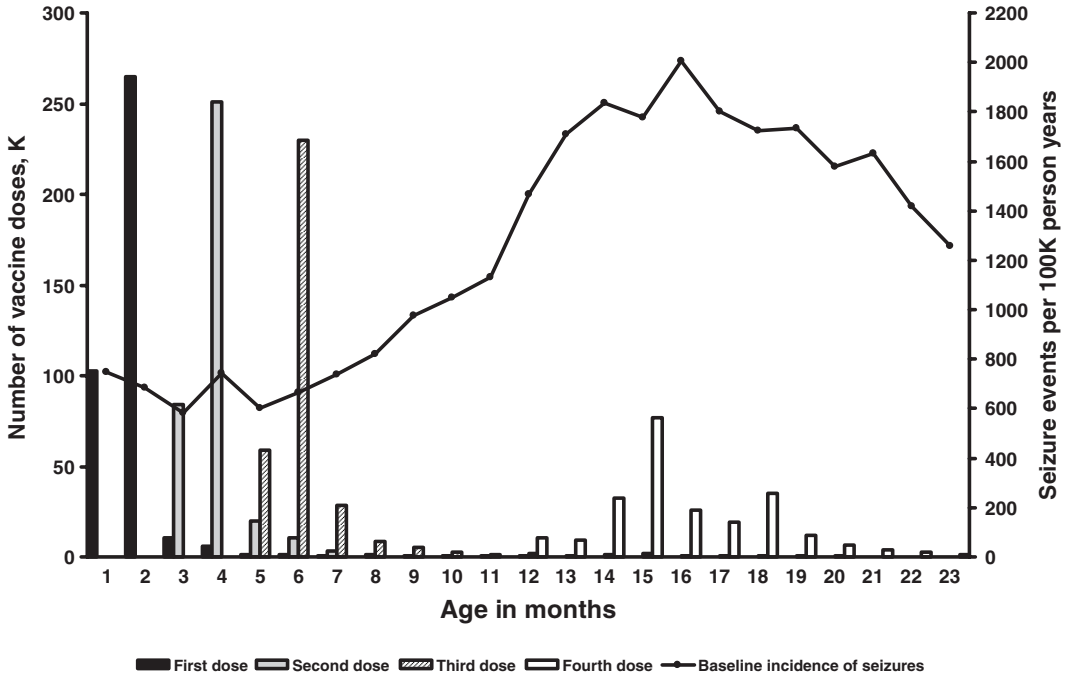

FIGURE 1
Administration of DTaP and baseline incidence of seizures, by age of child: 7 MCOs of the Vaccine Safety Datalink Project, United States, 1997–2006. Note the baseline seizure incidence peaks and plateaus around the fourth vaccine dose.

TABLE 1 Number of Seizure Diagnoses Coded at the ED and Hospital Settings

ICD-9-CM Code	Outcome	EDs (n = 4557), n (%)	Hospitals (n = 2634), n (%)	EDs and Hospitals (n = 7191), n (%)
333.2	Myoclonus	23 (<1)	40 (2)	63 (<1)
345[a]	Epilepsy	104 (2)	366 (14)	470 (7)
777.9	Convulsions in newborn	4 (<1)	48 (2)	52 (<1)
780.31, 780.32	Febrile convulsions	3059 (67)	466 (18)	3525 (49)
780.39	Other convulsions	900 (20)	1372 (52)	2272 (32)
780.3[b]	Convulsions	467 (10)	342 (13)	809 (11)

[a] Any ICD-9-CM code with prefix "345."
[b] Diagnoses available as 4-digit ICD-9-CM code 780.3.

(Table 2), at times when the comparison (baseline) incidence of seizures peaked and plateaued as well (Fig 1). Age was 1 of the covariates significantly associated with seizures in the multivariate model. Other covariates that were significantly associated with seizures included gender, MCO, calendar year, season of the year, and receipt of MMR or MMRV within 8 to 14 days before the seizure event. The IRR of seizures within 0 to 3 days of receiving DTaP across all doses was 0.87 (95% CI: 0.72–1.05) in cohort and 0.91 (95% CI: 0.75–1.10) in SCCS analyses, after adjustments for all variables described in the Methods section. In both cohort (Table 2) and SCCS (Table 3) analyses stratified by dose number and postvaccination risk interval, receipt of DTaP was not associated with a significantly increased risk for seizures.

DISCUSSION

Our study did not observe a significantly increased risk for seizures within 0 to 3 days after DTaP vaccination for various dose numbers and risk intervals. Overall, 433 654 children were observed for 603 098 person-years in the cohort analyses. The large cohort size increases the precision of IRR estimates and the chance of detecting a positive association—the study has at least 80% power to detect a true IRR of 2.09 for seizures within 0 to 3 days after each DTaP dose.[20] By contrast, published studies have found a relative risk (RR) of 3.3 (95% CI: 1.4–8.2) for seizures within 7 days of DTP administration.[2] Specifically, the increased risk after DTP was limited to febrile seizures during the 0 to 3 days after the third dose (RR: 3.0 [95% CI: 1.6–5.5])[3] or on the same day of any doses (RR: 5.70 [95% CI: 1.98–16.42]).[4] The findings in our study provide reassuring evidence on the safety of DTaP with respect to seizures.

Our results were consistent regardless of the analytical strategy. The majority of our analyses demonstrated a negative association between seizures and DTaP, and the effects were of similar magnitude using the risk-interval cohort (Table 2) or SCCS (Table 3) method. Because children are more likely to be vaccinated when consid-

TABLE 2 Incidence Rates and IRRs in the Risk-Interval Cohort Analysis of Seizures After Acellular Pertussis Vaccination

Dose	Days After Vaccination	No. of Seizure Events	Person-years[a]	IR (95% CI)[b]	Adjusted IRR (95% CI)[c]
All	0–3	112	14 708	761 (633–916)	0.87 (0.72–1.05)
	0	28	3677	761 (526–1103)	0.87 (0.60–1.26)
	1–3	84	11 031	761 (615–943)	0.87 (0.70–1.08)
First	0–3	28	4253	658 (455–954)	0.99 (0.68–1.44)
	0	9	1063	847 (440–1627)	1.27 (0.66–2.45)
	1–3	19	3190	596 (380–934)	0.90 (0.57–1.41)
Second	0–3	20	4097	488 (315–757)	0.72 (0.46–1.12)
	0	5	1024	488 (203–1173)	0.72 (0.30–1.74)
	1–3	15	3073	488 (294–810)	0.72 (0.43–1.20)
Third	0–3	24	3781	635 (425–947)	0.87 (0.58–1.30)
	0	6	945	635 (285–1413)	0.87 (0.39–1.94)
	1–3	18	2836	635 (400–1007)	0.87 (0.54–1.38)
Fourth	0–3	40	2577	1552 (1139–2116)	0.89 (0.65–1.22)
	0	8	644	1242 (621–2483)	0.71 (0.36–1.43)
	1–3	32	1933	1656 (1171–2341)	0.95 (0.67–1.35)
Comparison[d]	NA	7079	588 390	1203 (1175–1231)	Referent

IR indicates incidence rate; NA, not applicable.

[a] Converted from person-days.

[b] Number of seizure events per 100 000 person-years.

[c] Unconditional Poisson regression model adjusted for MCOs, gender, calendar year, season, age, and receipt of MMR or MMRV within 8 to 14 days.

[d] Unexposed person-time composed of all observation periods outside the predefined risk intervals.

TABLE 3 IRRs in the SCCS Analysis of Seizures After Acellular Pertussis Vaccination

Dose	Days After Vaccination	No. of Seizure Events	Person-years[b]	Adjusted IRR (95% CI)[c]
All	0–3	112	204	0.91 (0.75–1.10)
	0	28	51	0.91 (0.63–1.32)
	1–3	84	153	0.91 (0.73–1.13)
First	0–3	28	55	1.02 (0.70–1.50)
	0	9	14	1.32 (0.68–2.54)
	1–3	19	41	0.93 (0.59–1.46)
Second	0–3	20	54	0.75 (0.48–1.17)
	0	5	14	0.75 (0.31–1.81)
	1–3	15	41	0.75 (0.45–1.25)
Third	0–3	24	53	0.90 (0.60–1.35)
	0	6	13	0.90 (0.40–2.01)
	1–3	18	39	0.90 (0.56–1.43)
Fourth	0–3	40	42	0.95 (0.69–1.29)
	0	8	10	0.76 (0.38–1.51)
	1–3	32	31	1.01 (0.71–1.43)

[a] Data were from 5205 case patients (7191 seizure events) with a total observation period of 3 283 753 person-days (8890 person-years).

[b] Converted from person-days.

[c] Conditional Poisson regression model adjusted for calendar year, season, age, and receipt of MMR or MMRV within 8 to 14 days.

ered healthy by parents and physicians, this negative association could reflect confounding from either avoidance or delay of DTaP vaccination by those who are predisposed to or have had recent seizures.[21] Compared with the cohort method, the SCCS method avoids potential confounding that may result from comparing patients with different baseline risks for seizures and is highly efficient because it requires information on case-patients only[19]; however, a major advantage of the cohort method is the ability to calculate the baseline incidence of seizures from the unexposed cohort. The baseline incidence of seizures varies approximately threefold between the ages of 6 and 23 months (Fig 1), and age is also related to vaccination times. Although the unadjusted incidence of seizures in the postvaccination 0 to 3 days was higher after the fourth dose of DTaP, we were able to adjust the IRRs for confounding by age in the Poisson regression models and did not observe an increased risk for seizures after the fourth dose.

The findings in this study are subject to at least 3 limitations. First, the study used automated data on immunizations that do not always agree with data from medical records; however, VSD automated vaccination data have been found to have high sensitivity (range: 82%–98%) and predictive positive value (range: 83%–99%) relative to vaccinations documented in medical records.[17] Second, only seizures that presented to the ED or in association with a hospital discharge were examined; nevertheless, this restriction was justifiable. Seizures coded in the VSD outpatient setting are likely to be management or follow-up for a previous seizure event or visit for another reason among children with a history of seizure disorders, which rarely represent true acute seizure events.[18] In addition, the proportion of seizures that were not brought to medical attention was expected to be small because of the potential severity of seizure events. Finally, DTP is associated with an increased risk for febrile but not nonfebrile seizures[3,4]; however, in our study, febrile seizures were not completely identified. The presence of fever may be poorly recorded in automated data, and restricting the analysis to codes of simple (780.31) and complex (780.32) febrile convulsions is likely to miss true febrile seizures, limiting the generalizability and power. Febrile seizures typically occur in children who are aged 6 to 36 months with a peak at 18 months[22]; therefore, seizures that are coded between ages 12

and 23 months are highly predictive of true acute febrile seizures (I. Shui, MPH, written, personal communication). The negative association between all seizures and DTaP supports the absence of an increased risk for febrile seizures after receipt of DTaP at this age group. Nevertheless, for children who are aged 6 weeks to 11 months, an unbiased assessment of the risk for febrile seizures after DTaP vaccination would require reviews of medical records to validate the diagnoses.

In the United States, public concerns about the safety of DTP have led to the establishment of modern vaccine safety infrastructure for monitoring and compensation of adverse events. The National Childhood Vaccine Injury Act of 1986[23] was enacted in response to a large number of lawsuits, withdrawal from the market of vaccines by several DTP manufacturers, and a substantial rise in vaccine prices.[6] The National Childhood Vaccine Injury Act provisions required health care providers and manufacturers to report certain adverse events after specific immunizations to the Vaccine Adverse Event Reporting System[8]; established a committee from the Institute of Medicine to review the existing evidence on vaccine adverse events[1,24]; and created the National Vaccine Injury Compensation Program, a no-fault program to limit manufacturer liability by providing compensation to people who are found to be injured by certain vaccines.[25] Continued postlicensure safety surveillance and research when acellular pertussis vaccines are used widely in populations is essential to assist policymakers in assessing needs for improvement in vaccine preparations or for changes in vaccination strategy.

CONCLUSIONS

Our study is the largest postlicensure population-based study to date to examine the association between seizures and DTaP. Among children aged 6 weeks to 23 months, no increased risk for seizures in the 0 to 3 days after DTaP vaccination was observed. Safety concerns about DTP resulted in declining public trust in vaccines, which affected the immunization programs.[5,6] The use of DTaP has replaced the use of DTP in the United States.[13] Our findings provide reassuring evidence that the vaccine is not associated with acute seizure events and is safe for routine immunization in early childhood.

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